

PCT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|---|---|--|---|
| Applicant's or agent's file reference P7057W0 CTH | FOR FURTHER ACTION | | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/GB 00/ 02428 | International filing date (day/month/year) 23/06/2000 | (Earliest) Priority Date (day/month/year) 25/06/1999 | |
| Applicant IMERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE | | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

P B 00/02428

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/31 C07K14/33 A61K39/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | FIGUEIREDO D ET AL.: "Characterization of recombinant tetanus toxin derivatives suitable for vaccine development" INFECTION AND IMMUNITY, vol. 63, no. 8, August 1995 (1995-08), pages 3218-3221, XP002151794 abstract figures 1,3; table 1 page 3221, left-hand column, line 4-40 --- -/-- | 1-14 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 November 2000

Date of mailing of the international search report

22/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/ISA 00/02428

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | HALPERN J L ET AL.: "Characterization of the receptor-binding domain of tetanus toxin" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 15, 25 May 1993 (1993-05-25), pages 11188-11192, XP002151795 cited in the application | 1-8, 11-16 |
| Y | abstract figures 1,3 | 9,10 |
| Y | EP 0 209 281 A (WELLCOME FOUND) 21 January 1987 (1987-01-21) cited in the application examples 4,8,9 claims 14-16 figure 2 | 9,10 |
| A | SHAPIRO R E ET AL.: "Identification of a ganglioside recognition domain of tetanus toxin using a novel ganglioside photoaffinity ligand" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 48, 28 November 1997 (1997-11-28), pages 30380-30386, XP002151796 cited in the application abstract | 1,15,16 |
| A | ANDERSON R ET AL: "Immunization of mice with DNA encoding fragment C of tetanus toxin" VACCINE, vol. 15, no. 8, 1 June 1997 (1997-06-01), pages 827-829, XP004075662 abstract page 827, left-hand column, line 10-28 page 828, right-hand column, line 29-35 | 1,9,10 |
| A | WO 94 00487 A (US ARMY) 6 January 1994 (1994-01-06) page 4, line 18 -page 5, line 6 example 5 | 10,11, 13-15 |
| A | UMLAND T C ET AL.: "Structure of the receptor binding fragment HC of tetanus toxin" NATURE STRUCTURAL BIOLOGY, vol. 4, no. 10, October 1997 (1997-10), pages 788-792, XP000952554 cited in the application abstract page 789, right-hand column, line 1 -page 790, left-hand column, line 22 | 1,15,16 |
| | --- | |
| | -/-- | |

INTERNATIONAL SEARCH REPORT

International Application No

P B 00/02428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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|------------|---|-----------------------|
| A | HALPERN J L ET AL.: "Neurospecific binding, internalization, and retrograde axonal transport" CURR. TOP. MICROBIOL. IMMUNOL., vol. 195, 1995, pages 221-241, XP000960426 the whole document ---- | 1-16 |
| T | SINHA K ET AL.: "Analysis of mutants of tetanus toxin HC fragment: ganglioside binding, cell binding and retrograde axonal transport properties" MOLECULAR MICROBIOLOGY, vol. 37, no. 5, September 2000 (2000-09), pages 1041-1051, XP000952564 the whole document ----- | 1-16 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/02428

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| EP 0209281 A | 21-01-1987 | AU 5941486 A DK 307986 A ES 2000255 A FI 862761 A JP 62051994 A ZA 8604805 A | 08-01-1987 29-12-1986 01-02-1988 29-12-1986 06-03-1987 24-02-1988 |
| WO 9400487 A | 06-01-1994 | AU 4545393 A US 5601826 A | 24-01-1994 11-02-1997 |

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00839 A1

- (51) International Patent Classification⁷: C12N 15/31, C07K 14/33, A61K 39/08
- (21) International Application Number: PCT/GB00/02428
- (22) International Filing Date: 23 June 2000 (23.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9914861.1 25 June 1999 (25.06.1999) GB
- (71) Applicant (for all designated States except US): IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE [GB/GB]; Sherfield Building, Exhibition Road, London SW7 2AZ (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FAIRWEATHER, Neil, Fraser [GB/GB]; 1 The Drive, Bexley, Kent DA3 3DH (GB). SINHA, Katharine [GB/GB]; Imperial College, Dept. of Biochemistry, South Kensington, London SW7 2AY (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- With international search report.
 - Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TETANUS TOXIN POLYPEPTIDES

(57) Abstract: A polypeptide is provided which polypeptide comprises tetanus toxin (TeNT) fragment C, or an immunogenic fragment thereof, which tetanus toxin fragment C, or immunogenic fragment thereof comprises a mutation in a loop region, which mutation results in: a reduction in the binding of the tetanus toxin fragment C, or immunogenic fragment thereof, to gangliosides; and/or a reduction in the binding of the tetanus toxin fragment C, or immunogenic fragment thereof, to primary motoneurons; and/or a reduction in the ability of the tetanus toxin fragment C, or immunogenic fragment thereof, to undergo retrograde transport.

WO 01/00839 A1

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/GB 00/02428

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C07K14/33 A61K39/08

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, EMBL

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 November 2000

Date of mailing of the international search report

22/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | HALPERN J L ET AL.: "Characterization of the receptor-binding domain of tetanus toxin" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 15, 25 May 1993 (1993-05-25), pages 11188-11192, XP002151795 cited in the application | 1-8, 11-16 |
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| A | ANDERSON R ET AL: "Immunization of mice with DNA encoding fragment C of tetanus toxin" VACCINE, vol. 15, no. 8, 1 June 1997 (1997-06-01), pages 827-829, XP004075662 abstract page 827, left-hand column, line 10-28 page 828, right-hand column, line 29-35 | 1,9,10 |
| A | WO 94 00487 A (US ARMY) 6 January 1994 (1994-01-06) page 4, line 18 -page 5, line 6 example 5 | 10,11, 13-15 |
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| | --- -/- | |

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/GB 00/02428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | HALPERN J L ET AL.: "Neurospecific binding, internalization, and retrograde axonal transport" CURR. TOP. MICROBIOL. IMMUNOL., vol. 195, 1995, pages 221-241, XP000960426 the whole document --- | 1-16 |
| T | SINHA K ET AL.: "Analysis of mutants of tetanus toxin HC fragment: ganglioside binding, cell binding and retrograde axonal transport properties" MOLECULAR MICROBIOLOGY, vol. 37, no. 5, September 2000 (2000-09), pages 1041-1051, XP000952564 the whole document ----- | 1-16 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02428

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 0209281 A | 21-01-1987 | AU 5941486 A | 08-01-1987 |
| | | DK 307986 A | 29-12-1986 |
| | | ES 2000255 A | 01-02-1988 |
| | | FI 862761 A | 29-12-1986 |
| | | JP 62051994 A | 06-03-1987 |
| | | ZA 8604805 A | 24-02-1988 |
| WO 9400487 A | 06-01-1994 | AU 4545393 A | 24-01-1994 |
| | | US 5601826 A | 11-02-1997 |

Figure 1



1/2

2/2

Figure 2

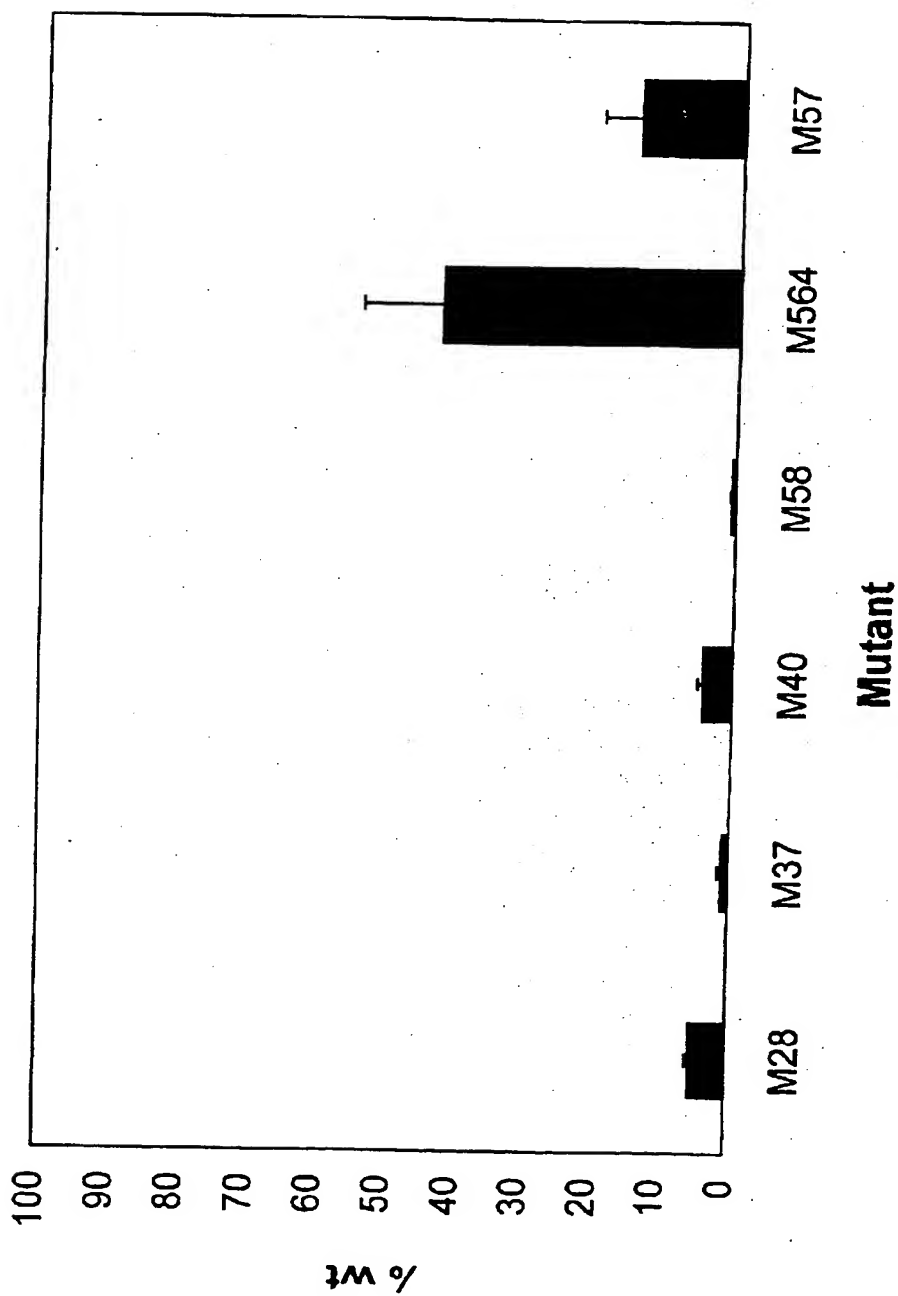
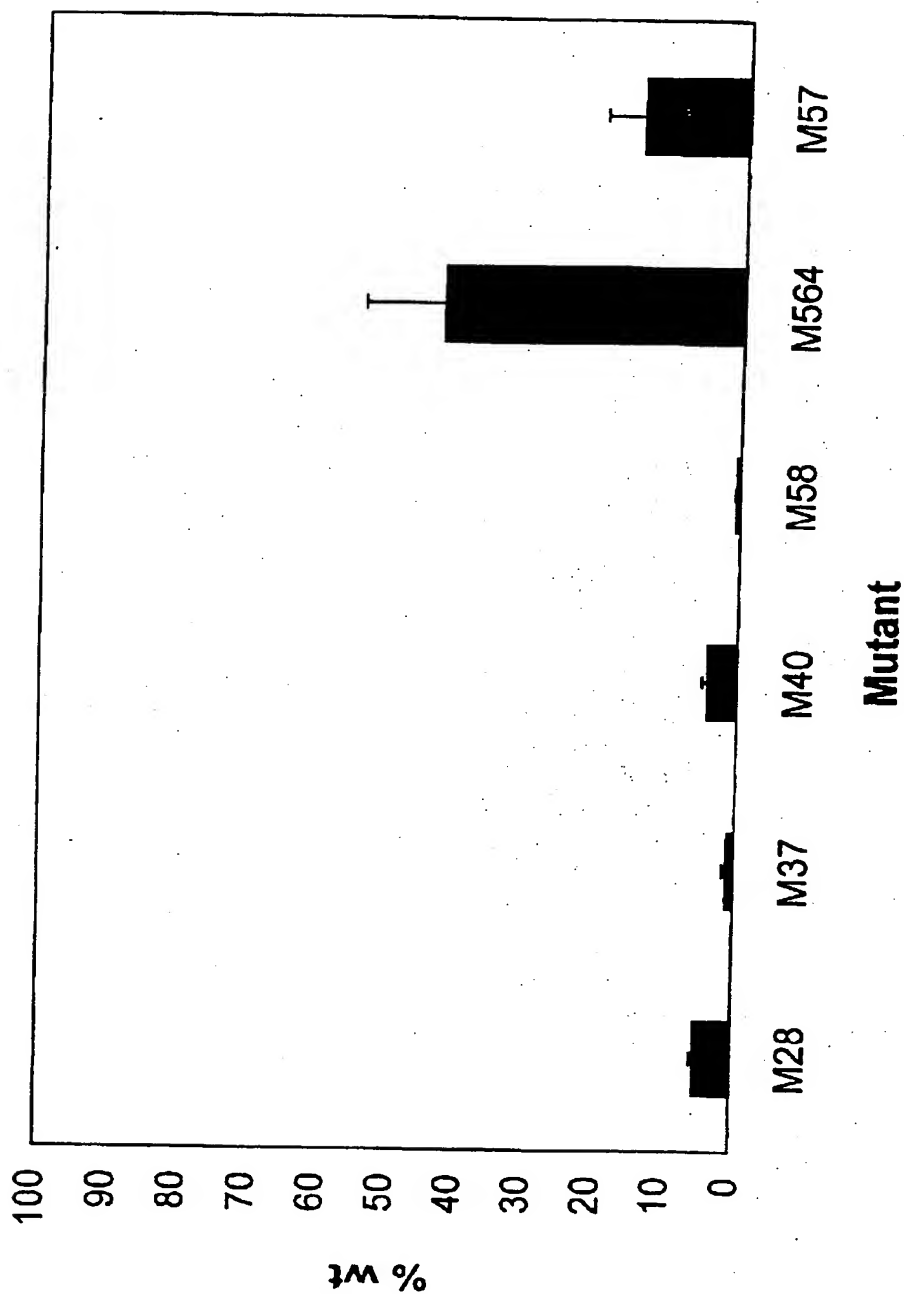


Figure 1



2/2


Figure 2



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | | |
|--|--|--|---|
| Applicant's or agent's file reference P7057WQ CTH | | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/GB00/02428 | International filing date (day/month/year) 23/06/2000 | Priority date (day/month/year) 25/06/1999 | |
| International Patent Classification (IPC) or national classification and IPC C12N15/31 | | | |
| Applicant <u>IMPERIAL</u> <u>IMPERIAL</u> COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE | | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application | | | |
| Date of submission of the demand 05/01/2001 | | Date of completion of this report 18.09.2001 | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | | Authorized officer Huber, A Telephone No. +49 89 2399 8173 | |



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02428

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-33 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

Sequence listing part of the description, pages:

1-9, filed with the letter of 11.08.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02428

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 11, 13, 14 (IA).

because:

- ☒ the said international application, or the said claims Nos. 11, 13, 14 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02428

1. Statement

| | | | |
|-------------------------------|------|--------|------------------|
| Novelty (N) | Yes: | Claims | 4 |
| | No: | Claims | 1-3, 5-9, 15, 16 |
| Inventive step (IS) | Yes: | Claims | 4 |
| | No: | Claims | 10-14 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 12, 15, 16 |
| | No: | Claims | |

2. Citations and explanations **see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 11, 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the above claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: FIGUEIREDO D ET AL.: 'Characterization of recombinant tetanus toxin derivatives suitable for vaccine development' INFECTION AND IMMUNITY, vol. 63, no. 8, August 1995 (1995-08), pages 3218-3221, XP002151794
- D2: HALPERN J L ET AL.: 'Characterization of the receptor-binding domain of tetanus toxin' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 15, 25 May 1993 (1993-05-25), pages 11188-11192, XP002151795 cited in the application

2. D1 discloses recombinant tetanus toxin derivatives suitable for vaccine development. Immunogenic derivatives of fragment C that have lost the ability to bind neurons and which lack C-terminal amino acids are described (e.g. TetC 1-180; TetC 1-271).

The polypeptide of Claim 1 is defined as comprising fragment C or an immunogenic fragment thereof, wherein said fragment C (or immunogenic fragment thereof) **comprises** a mutation in a loop region, thus the mutation must not be limited to a loop region.

The immunogenic mutants of D1 are also mutated within a loop region and exhibit reduced neuron binding.

The subject-matter of Claims 1-3 and 5-9 is therefore anticipated by the teaching of D1 (Art. 33(2) PCT).

Claims 10-14 are directed to a vaccine comprising a polypeptide of Claims 1-14, a polynucleotide according to Claim 5 or a vector according to Claim 6, methods of treating, preventing or reducing the susceptibility to *C. tetani* infection by administration of the polypeptide, polynucleotide or vector, the use thereof for preparing antibodies, a method for producing antibodies and a method of treating *C. tetani* infection by administration of said antibodies. The use of the fragment C derivatives of D1 for vaccine development, in particular of those derivatives that do not bind neurons is clearly suggested in D1. The subject-matter of Claim 10-14 therefore lacks the required inventive step (Art. 33(3) PCT).

D2 describes the involvement of the carboxy-terminal half of heavy chain (C fragment) of tetanus toxin in ganglioside and neuron binding.

Deletion of 10 or more C-terminal amino acids resulted in a complete loss of ganglioside binding. Deletion mutant Hc1-435 comprises deletion of at least one amino acid residue within a loop region (aa 1282). D2 is therefore novelty-destroying for the subject-matter of Claims 1-3, 5, 15 and 16.

Claim 4 is directed to specific deletion mutants of TeNT fragment C, which have neither been disclosed nor rendered obvious in the cited documents. Novelty and inventive step of the subject-matter of Claim 4 are therefore acknowledged.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02428

Re It m VIII

Certain observations on the international application

Claim 16 is directed to a polypeptide produced by the method of Claim 15. Claim 15 is, however, not directed to a method of producing a polypeptide but concerns a method for reducing the binding affinity of a TeNT fragment C polypeptide comprising modifying one or more amino acids of said polypeptide. Claim 16 is therefore not correctly dependent on Claim 15. It should also be noted that a polypeptide with reduced binding affinity to gangliosides in which one or more amino acids in a surface exposed loop region of TeNT fragment C are modified is already covered by Claim 1. Claim 16 therefore appears to be redundant.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

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| Date of mailing (day/month/year) 19 February 2001 (19.02.01) | |
| International application No. PCT/GB00/02428 | Applicant's or agent's file reference P7057WO CTH |
| International filing date (day/month/year) 23 June 2000 (23.06.00) | Priority date (day/month/year) 25 June 1999 (25.06.99) |
| Applicant FAIRWEATHER, Neil, Fraser et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
05 January 2001 (05.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer <p style="text-align: center;">Pascal Piriou</p> Telephone No.: (41-22) 338.83.38 |
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